REMARKS

I. Status of the claims and Support for the Amendment

Claim 3 is cancelled.

Claims 1, 9, 14, 18, and 19 are currently amended.

Claims 1, 2, and 4-22 are currently pending.

Support for the amendment of the claims is found in the specification at page 12, line 25 through page 13, line 5, at page 14, lines 1-10, and at page 25, lines 15-17. Applicant explicitly reserves the right to pursue any canceled material in one or more continuation or divisional applications. The Specification is amended to correct typographical errors in the last four rows of the right-most column of Table 1.

II. Formalities in the Specification

The Examiner has noted the use of the trademark "TWEEN®80" in the Specification. In response to the Examiner's requirement, the Specification is amended to correctly use the trademark "TWEEN®80" by capitalizing it where it appears in the specification. Applicant believes that this amendment overcomes the Examiner's objection to the Specification.

III. Rejection under 35 U.S.C. §112

Claims 9, 14, 18, and 19 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

A. Claim 9 is rejected as allegedly being indefinite for reciting for reciting "is comprised of." The Examiner suggest that the claim would be clear if it recited "comprising" instead of "is comprised of." Applicant responds as follows.

Applicant respectfully disagrees with the Examiner's assessment that use of the phrase "is comprised of" renders claim 9 indefinite. Nevertheless, in order to expedite allowance of the claims, as amended claim 9 now recites "comprises" instead of "is comprised of." Applicant

believes that this overcomes the Examiner's rejection. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

B. Claim 18 is rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for reciting the phrases "desired physiological response" and "active in an animal." Applicant respectfully traverses.

As amended claim 18 now recites "[a] method of administering somatotropin to a susceptible animal comprising...a somatotropin biologically-active in the animal . . . ." Applicant asserts that as amended claim 18 is now clearly definite. One of ordinary skill in the art would clearly know how to "parenterally" administer a somatotropin as the claim requires. Furthermore, at page 14, lines 1-10 the Specification clearly defines the term "biologically-active" so that one of ordinary skill in the art would unequivocally find the limitations of claim 18 to be clear and definite. Consequently, Applicant believes that the rejection of claim 18, under 35 U.S.C. §112, second paragraph, has been overcome and should be withdrawn.

C. Claims 14 and 19 are rejected under 35 U.S.C. §112, second paragraph for the use of the term "TWEEN®80." Applicant responds as follows.

As currently amended claims 14 and 18 no longer recite the offending term. Given that the term "TWEEN®80" was only cited parenthetically, Applicant contends that this term was not necessary to define the invention and, therefore, its removal from the claim does not alter the scope of the claims. In view of this amendment, Applicant believes that the rejection of claims 14 and 19 under 35 U.S.C. §112, second paragraph, has been overcome and should be withdrawn.

D. Claim 18 is rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled. The Examiner asserts that "[c]laim 18 recites, 'desired physiological response' and

'active in an animal', but do[es] not provide any teachings in the instant specification [sic] as to how to achieve these responses (how to use the invention)." Applicant respectfully traverses.

As currently amended claim 18 now recites in pertinent part:

[a] method of administering somatotropin to a susceptible animal comprising: parenterally administering to the animal a biocompatible composition of matter comprising:

a) a somatotropin, biologically-active in the animal. . . (emphasis added).

In view of this amendment, Applicant asserts that currently amended claim 18 is described in the Specification sufficiently to enable one of skill in the art to "use the invention." One of skill in the art would clearly understand how to "parenterally administer" the recited composition to an animal. Furthermore, at page 14, lines 1-10, the Specification explicitly defines the term "biologically-active" so that one of skill in the art would immediately understand the metes and bounds of the current claim. That is, in view the definition of "biologically-active" provided at page 14 of the Specification, the ordinarily skilled artisan would have no difficulty determining whether a particular somatotropin is within scope of the claims.

Consequently, in view of the amendment of claim 18 and in further view of the foregoing explanation, Applicant believes that the rejection of claim 18 under 35 U.S.C. §112, first paragraph, has been overcome and should be withdrawn.

IV. Rejection under 35 U.S.C. §102

Claims 1, 5, 10, 15 and 18-20 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Magruder (U.S. Pat. No. 5,037,420). The Examiner states that:

> Magruder teaches porcine, bovine, equine, and human growth promoting hormone, column 13, lines 66-68 and column 14, line 1. Magruder discloses somatotropin in column 14, line 11. Magruder also teaches a pharmaceutical carrier composed of the agent, a buffer and a surfactant, column 14, lines 39-40.

> Magruder's buffer can comprise sodium phosphate monobasic or sodium phosphate dibasic, column 15, lines 36-37. Magruder discloses surfactants such as polyoxyethylene sorbitan monooleate, polyoxyethylene stearate and Tween 80, among others, column 15, lines 58, 59, 61, 62 and 68. Magruder teaches a non-aqueous carrier composed of wax, column 18, line 6.

Applicant respectfully traverses.

Firstly, Applicant notes that the purpose of the "wax" in Magruder is not that of a "carrier". At the passage cited by the Examiner, *i.e.*, at column 18, lines 5 and 6, Magruder recites: [i]n a presently preferred embodiment, layer **27** comprises a wax." Magruder then goes on to recite that preferred waxes exhibit "a melting point or a solidification point of about 45° C or higher, usually 45° C to 110° C" (Magruder column 18, lines 7 and 8). The purpose of the "layer" is described in Magruder at column 7 and shown in the figures. Magruder recites that:

> [c]ompartment **18** optionally comprises a layer **27**, represented by horizontal lines, which layer **27** is positioned between the beneficial agent formulation and the expandable driving member **25**. Layer **27**, in a presently preferred embodiment comprises a composition that is substantially impermeable to the passage of fluid and it serves to restrict the passage of fluid present in the expandable driving member into the beneficial agent formulation; and it operates to essentially maintain the integrity of the beneficial agent layer and the driving layer.

Magruder, col. 7, ll. 53-68 (emphasis added).

Applicant believes that at least two things are clearly shown by the description at columns 7 and 18 of Magruder. First, the "wax" in the Magruder invention serves as a barrier, not a carrier. Second, the wax is not fluid under delivery conditions (indeed Magruder states that the wax should be solid at temperatures from 45 °C to 110 °C. Thus, the Magruder disclosure differs from the instant invention in at least two respects. First, in Magruder the somatotropin is not "suspended in a substantially non-aqueous hydrophobic carrier" as required by the current claims. Indeed, contrary to being suspended in the wax, the purpose of the wax is to be an impermeable barrier between the somatotropin and "the expandable driving member." Second,

the invention described in Magruder is not "fluidly injectable at 25 °C." Instead the Magruder invention is a solid with the wax portions specific purpose being to prevent the "passage of a fluid."

For the reasons described above, Applicant asserts that Magruder does not anticipate the instantly pending claims. Therefore, the rejection of the claims under 35 U.S.C. §102(b), as being anticipated by Magruder, has been overcome and should be withdrawn.

V. Rejection under 35 U.S.C. §103

A. Claims 1, 5, 8, 10-12, and 14-22 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Magruder in view of Steber (U.S. Pat. No. 5,801,141). Magruder is cited for essentially the reasons cited, *supra*, in the rejection under 35 U.S.C. §102(b). Steber is cited as "teaching admixing somatotropin with a mixture of oxo-acid salts . . . ." The Examiner further alleges that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have added the oxo-acid salts of Steber to the composition disclosed by Magruder, because Steber teaches this method of elevating and maintaining elevated blood levels of somatotropin column 21, claim 26." Applicant respectfully traverses.

MPEP Chapter 700 sets out the requirements for establishing a *prima facie* case of obviousness. Chapter 700 states, in pertinent part that:

> [t]o establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (emphasis added).

MPEP 706.02(j) (emphasis added). Applicant asserts that the combination of the cited references to meet the criteria of *Vaeck.*

As discussed in response to the rejection of the claims under 35 U.S.C. §102(b) Magruder does not describe a composition which is "suspended in a substantially non-aqueous hydrophobic carrier," *a fortiori*, it does not describe such a composition that is "fluidly injectable at 25 °C." Moreover, Applicant contends that there is nothing in Magruder which would suggest the value of such features to one of ordinary skill in the art.

Applicant notes that Steber is cited specifically to demonstrate the admixture of oxo-acid salts. It is Applicant's position that the combination of Magruder and Steber does nothing to render the instantly pending claims obvious.

In fact, Steber specifically "teaches away" from the instantly pending claims. Steber teaches an implant which comprises a composition comprising, *inter alia*, "about 10% to about75% of a fat, a wax, or a mixture thereof . . . ." (Steber, col. 1, ll.43-44). Steber further recites that: "[w]axes and fats which are suitable for use in the composition of the present invention in general have melting points higher than 40° C" (Steber col. 6, ll. 4-6, emphasis added).

Thus, the combination of Magruder and Steber provides no teaching or suggestion that would motivate one of ordinary skill in the art to provide an invention within the scope of the currently pending claims. The combination of Magruder and Steber teaches a composition that is solid at 25°C, indeed one that is solid at all temperatures below 40°C. Steber specifically teaches that waxes or fats that have melting points below 40°C are unsuitable for use in the Steber invention and, as noted above, Magruder teaches that waxes are to be used as a solid barrier to prevent fluid flow. Thus the combination of Magruder and Steber teaches away from

the instantly pending claims and therefore fails to meet any, let alone all of the requirements of *Vaeck*. Accordingly, Applicant respectfully asserts that the rejection of the claims over the combination of Magruder and Steber has been overcome and should be withdrawn.

B. Claims 2 and 3 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Magruder in view of Steber, as applied to claims 1, 14, and 18, *supra*, and in further view of Scarborough (U.S. Pat. No. 6,162,258). The Examiner states that while "Magruder discloses a biological implant but does not mention the temperature of the implant, absent some evidence to the contrary, the implant would be implanted in an animal (approximately 37-39[°]C." The Examiner further states that "Magruder in view of Steber does not teach...non-ionic surfactants." Thus Scarborough is cited as teaching surfactant/somatotropin mixtures. Finally, the Examiner asserts that:

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have added the non-ionic surfactants of Scarborough to the composition disclosed by Magruder in view of Steber in order to enhance the bioavailability of somatotropin in the composition, because Scarborough teaches biocompatibility in the healing response, column 3, lines 55 and 61.

Applicant respectfully traverses.

As shown in part "A.," above, the combination of Magruder and Steber fails to establish a *prima facie* case of obviousness for the instantly pending claims. Additionally, Applicant notes that the temperature limitation in the claims do not limit the *temperature* of the composition, rather it limits *melting point* of the composition, thus the Examiner's reference to temperature is moot.

Applicant contends that Scarborough adds nothing to the combination of Magruder and Steber to alter this result. Scarborough does not describe somatotropin compositions rather Scarborough describes a method for preserving and rehydrating monolithic bone for use as a

bone graft. The surfactants cited by Examiner are included as part of an extensive laundry list (~80 compounds) of "mechanical strength-conserving agents" which can be used to treat the prepared bone fragment prior to lyophilization (*see*, col. 4, ll. 45 through col. 5, ll.31). Similarly, somatotropin is only included in the patent as part of a long laundry list of compounds that may, *optionally*, be added to the solution used to rehydrate the bone (*see,* col. 6, ll. 30-49). Thus, Scarborough cannot be accurately viewed as teaching or suggesting that a composition comprising a surfactant and somatotropin is desirable or advantageous. In fact, Scarborough does not even teach a composition comprising somatotropin and a surfactant. Rather, Scarborough lists both compounds as part long lists of possible agents that might, separately, be useful as components of separate solutions the surfactant for strengthening the bone and the somatotropin as an *optional* component of the rehydrating solution (meaning that somatotropin is not a necessary component).

Moreover, even if the surfactant and the somatotropin were selected from among the long lists disclosed, Scarborough teaches that they are added to the monolithic bone, not injected into an animal. The composition taught by Scarborough, then comprises the monolithic bone, which is certainly not "fluidly injectable" (instead, as Scarborough teaches, the monolithic bone must be surgically implanted).

In view of these facts, Applicant contends that there is nothing in the combination of Magruder, Steber, and Scarborough which teaches or suggests combining the references so as to obtain the instantly claimed invention. Consequently, Applicant asserts that the rejection of the claims as being unpatentable over the combination of these references has been overcome and should be withdrawn.

C. Claim 4 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Magruder in view of Steber, as applied to claims 1, 14, and 18, and in further view of Mitchell (U.S. Pat. No. 5,474,980, hereinafter "the '980 patent"). The Examiner concedes that Magruder and Steber "do not teach somatotropin...present as a zinc salt or complex." However, the Examiner contends that Mitchell "teaches somatotropin with preferred metals such as zinc, column 4, lines 51-52." For this reason the Examiner states that:

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have admixed the zinc of Mitchell to the composition disclosed by Magruder in view of Steber, in order to enhance the bioavailability of the somatotropin in the composition, because Mitchell teaches that certain metal-associated somatotropins are useful for prolonged parenteral release of such somatotropins, see abstract.

Applicant respectfully traverses.

As shown in part "A.," above, the combination of Magruder and Steber do not render the instant claims obvious. Applicant contends that the '980 patent does not change this result. The '980 patent describes compositions of bioactive peptides in a biocompatible oil. However, the '980 patent does not suggest including in that composition, as a first bioavailability enhancing constituent (BEC), a non-ionic surfactant. Nor does the '980 patent, taken either alone or in combination with Magruder and Steber, teach or suggest that it may be further advantageous to add one or more non-reducing carbohydrate(s) and/or one or more oxo-acid salt(s) to the composition, as a second BEC.

Moreover, for the reasons described in part "A." there is no suggestion provided by the combination of Magruder, Steber, and the '980 patent to combine the references so as to achieve the instantly claimed invention. Rather, Magruder and Steber specifically "teach away" from such combination. Therefore, in view of the claim amendments and the arguments presented,

Applicant believes that the instant rejection under 35 U.S.C. §103(a) has been overcome and should be withdrawn.

D. Claims 6 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Magruder in view of Steber, as applied to claims 1, 14, and 18, above, and further in view of Hamilton (U.S. Pat. No. 4,816,568). The Examiner asserts that:

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have added the polyol stabilizer of Hamilton to the composition disclosed by Magruder in view of Steber in order to enhance the bioavailability of the somatotropin in the composition, because Hamilton teaches that growth hormones may be admixed with various stabilizers to provide for the preservation of the soluble bioactivity of the growth hormone, see abstract.

Applicant respectfully traverses.

For the reasons cited above, Applicant has demonstrated that the combination of Magruder and Steber "teaches away" from the instantly pending claims. Applicant contends that the addition of Hamilton does nothing to alter this result.

Hamilton describes only mixtures of growth hormones and a "stabilizer" selected from a polyols, amino acids, a polymer of an amino acid, or derivatives of choline (*see*, col. 5, ll. 40-53). Hamilton teaches that the somatotropin compositions can be in a "liquid form or solution which is administered by subcutaneous injection," alternatively the "stabilized growth hormone formulation [can be] compressed into a tablet or pellet form . . ." (*see*, Hamilton col. 5, ll. 56-65). Hamilton further recites that:

> [w]hen an injectable form of the stabilized growth promoting formulation is desired, the stabilizer is first dispersed in an aqueous solution which can be stirred or shakened [sic] to bring about a more rapid solubilization of the stabilizer. After the aqueous solution of the stabilizer has been formed, the growth hormone is added.

(Hamilton, col. 4, line 67 through col. 5, line 5, emphasis added). Thus, Hamilton provides for either an aqueous solution of somatotropin or a solid composition of somatotropin. Hamilton

provides no teaching or suggestion that a composition "wherein the somatotropin and BEC are suspended in a substantially *non-aqueous* hydrophobic carrier" would be advantageous.

In contrast it is an important objective of the instant invention to protect the somatotropin from water, which reduces its stability. The instantly claimed invention accomplishes this objective by combining the somatotropin with one or more bioavailability enhancing constituents in a non-aqueous environment and maintaining this environment through injection by keeping the somatotropin suspended in the non-aqueous vehicle.

In view of the foregoing, Applicant contends that there is nothing in the combination of Magruder, Steber, and Hamilton which suggests any advantage for combining the teachings of those references so as to achieve the instantly claimed invention. On the contrary, the cited references "teach away" from the instantly claimed invention by teaching, in the alternative, aqueous solutions of somatotropin or somatotropin compositions which are solid at a temperature of 40°C, or event higher, and that are certainly solids at temperatures below 40°C. For these reasons, Applicant contends that the rejection of the instantly pending claims as being unpatentable over the combination of Magruder, Steber, and Hamilton has been overcome and should be withdrawn.

E. Claims 9 and 13 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Magruder in view of Steber, as applied to claims 1, 14, and 18, above and further in view of Mitchell (U.S. Pat. No. 5,739,108, referred to hereinafter as "the '108 patent"). The Examiner states that:

> Mitchell teaches that [sesame] oil and monostearate are useful for prolonged release of the somatotropin (see abstract).
>
> It would have been *prima facie* obvious to on of ordinary skill in the art at the time the invention was made to have formulated the composition disclosed by Storrs in view of Stern [sic] in the biocompatible oil/aluminum monostearate

> vehicles taught by Mitchell because Mitchell teaches that the oil/monostearate vehicles are useful for prolonged parental [sic] release of somatotropin *in vivo*.

Applicant respectfully traverses.

Applicant notes that Examiner has cited "Storrs and Stern" in the rejection. Applicant presumes that this is a typographical error (since Storrs and Stern are not further identified) and responds based on the assumption that the Examiner meant to referring to Magruder and Steber. If this assumption is in error, Applicant respectfully requests clarification.

In responding to the rejection Applicant notes that the '108 patent is a continuation of the '980 patent. Therefore, all arguments regarding the '980 patent (*see*, part "C.," *supra*) are equally applicable to the '108 patent, since they are based on exactly the same specification. Consequently, the arguments presented in part "C." apply *mutatis mutandis* to the rejection of claims 9 and 13. Specifically, the '108 patent does suggest adding one or more BEC's and the combination of Magruder and Steber "teaches away" from combining those references with the '108 patent to provide the instantly pending claims. Therefore, Applicant believes that the rejection of claims 9 and 13 (and the claims dependent therefrom) under 35 U.S.C. §103(a) has been overcome and should be withdrawn.

VI. Conclusion

In view of the foregoing Amendments (to the Specification and Claims) and in further view of the above Remarks, Applicant believes that all objections to and rejections of the current Application have been overcome. Consequently, Applicant asserts that the instant Application is in condition for immediate allowance. Accordingly, Applicant respectfully requests reconsideration of the instant Application and issuance of a Notice of Allowance therefor.

The Examiner is invited to contact the undersigned patent agent at (713) 787-1589 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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